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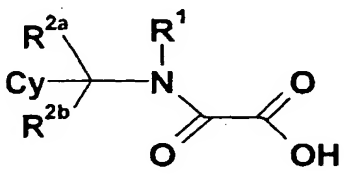
(54) Title: SUBSTITUTED METHYLENE AMIDE DERIVATIVES AS MODULATORS OF PROTEIN TYROSINE PHOSPHATASES (PTPS)



(I)

(57) Abstract: The present invention is related to substituted methylene amide derivatives of formula (I) and use thereof for the treatment and/or prevention of metabolic disorders mediated by insulin resistance or pyperglycemia, comprising diabetes type I and/or II, inadequate glucose tolerance, insulin resistance, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, obesity, polycystic ovary syndrome (PCOS). In particular, the present invention is related to the use of substituted methylene amide derivatives of formula (I) to modulate, notably to inhibit the activity of PTPs. Also the present invention relates to a method of treating diabetes type II, obesity and to regulate the appetite of mammals. The present invention is furthermore related to novel substituted methylene amide derivatives and method of preparation thereof. Formula (I).

WO 03/064376 A1

Substituted methylene amide derivatives as Modulators of Protein Tyrosine Phosphatases (PTPs)

Field of the invention

The present invention is related to substituted methylene amide derivatives of formula (I), in particular for the treatment and/or prevention of metabolic disorders mediated by insulin resistance or hyperglycemia, comprising diabetes type I and/or II, inadequate glucose tolerance, insulin resistance, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, obesity, polycystic ovary syndrome (PCOS). The compounds of this invention are particularly useful in the treatment of type II diabetes, obesity or the regulation of appetite. Specifically, the present invention is related to substituted methylene amide derivatives for the modulation, notably the inhibition of the activity of PTPs, in particular of PTP1B.

Background of the invention

The prevalence of insulin resistance in glucose intolerant subjects is well known. Reaven et al (*American Journal of Medicine*, 60, 80 (1976)) used a continuous infusion of glucose and insulin (insulin/glucose clamp technique) and oral glucose tolerance tests to demonstrate that insulin resistance exists in a diverse group of non-obese, non-ketotic subjects. These subjects ranged from borderline glucose tolerant to overt, fasting hyperglycemia. The diabetic groups in these studies included both insulin dependent (IDDM) and non-insulin dependent (NIDDM) subjects.

Coincident with sustained insulin resistance is the more easily determined hyper-insulinemia, which may be measured by accurate determination of circulating plasma insulin concentration in the plasma of subjects. Hyperinsulinemia may be present as a result of insulin resistance, such as is in obese and/or diabetic (NIDDM) subjects and/or glucose intolerant subjects, or in IDDM subjects, as a consequence of over injection of insulin compared with normal physiological release of the hormone by the endocrine pancreas.